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Fructose Metabolism

V. Catalytically Coupled Reactions[1]

ROBERT H. HERMAN, M.D., AND DAVID ZAKIM, M.D.

IN THE CHAIN of reactions converting fructose to lactic acid there exist certain enzymatic reactions which generate and utilize the cofactor pairs, NAD+-NADH, and ADP-ATP.[2] The reactions that utilize NAD+ to produce NADH can be regarded as coupled to the reactions that utilize NADH to produce NAD+. A similar relationship applies to ADP-ATP reactions. These sets of reactions are shown in Fig. 1.

Inherent in the concept of these coupled reactions is the idea that at a given level of cofactor concentration the rate of cofactor-pair production and utilization reaches a steady state. The reactions dependent on the cofactor pairs consequently become catalytically controlled by the steady state rate. Thus, the NAD+-NADH and ADP-ATP dependent reactions are catalytically coupled reactions.

Since the path from fructose to lactic acid uses both sets of cofactors each set regulates the other for a given concentration of each cofactor pair. *Reaction 2* is coupled with *reaction 5*. For a given level of NAD+ each of these reactions will assume a coupled reaction rate. However, in order for 1,3-diphosphoglyceric acid to reach pyruvate it must pass through *reactions 10* and *11*. The rates of these two reactions will be governed, in part, by the availability of ADP which can be generated from *reactions 6* and *7*. Thus, *reactions 6* and *7* can exercise control over *reactions 10* and *11* by regulating the level of ADP. *Reactions 10* and *11* can regulate *reactions 2* and *5* which in turn can control *reactions 6* and *7* by regulating the rate of removal of glyceraldehyde-3-phosphate.

These catalytically coupled reactions would appear to regulate the overall rate of conversion of fructose to lactic acid. The initial level of NAD+ would depend on its rate of formation from tryptophan, nicotinic acid, or nicotinamide, and its rate of degradation. It has been shown that the injection of tryptophan, nicotinic acid, or particularly nicotinamide into rats and mice leads to high hepatic levels of NAD+ (1–3). There also would be some transformation of NAD+ into NADP+. It has been shown that NADPH can inhibit NAD kinase which carries out this transformation and this may limit the formation of NADP+(4). This may explain why the injection of 7-^{14}C-nicotinamide into rats leads to slow equilibration of NADP+

[1] From the Metabolic Division, U. S. Army Medical Research and Nutrition Laboratory, Fitzsimons General Hospital, Denver, Colorado 80240.

[2] Abbreviations used are: NAD+ = nicotinamide adenine dinucleotide; NADH = reduced nicotinamide adenine dinucleotide; ADP = adenosine diphosphate; ATP = adenosine triphosphate; NADP+ = nicotinamide adenine dinucleotide phosphate; and NADPH = reduced nicotinamide adenine dinucleotide phosphate.

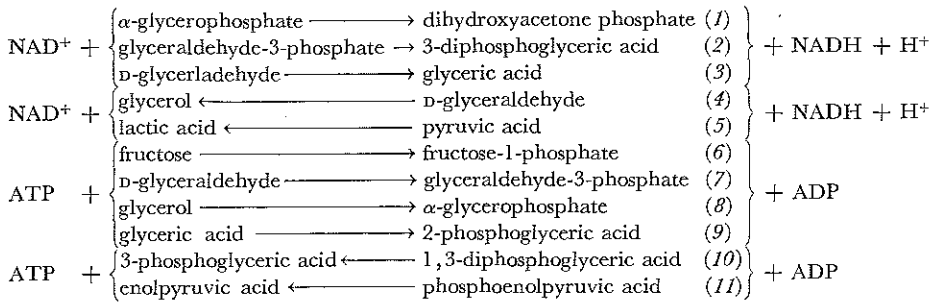

FIG. 1

and NADPH while NAD+ and NADH equilibrate much more rapidly (5). There would be utilization of NADH by mitochondrial systems with regeneration of NAD+ in turn. This in effect would be another set of catalytically coupled reactions with the utilization of ADP by the mitochondria to produce ATP.

The level of ATP would depend on the net rate of formation of ATP from the Embden-Meyerhof pathway, via oxidative phosphorylation in mitochondria, and through the de novo synthesis of ATP. It should be noted that ADP inhibits *reaction 6* (5).

The addition of NAD+ to rat liver homogenates enhances the utilization of both glucose and fructose (7). Addition of ATP and NAD+ does not greatly increase the utilization of glucose by either kidney or liver homogenates above the level seen with NAD+ alone. However, since these were crude homogenates there may have been potent ATPases present.

It has been shown that fructose increases the rate of ethanol oxidation (8–11). The infusion of both fructose and ethanol as compared to fructose alone in man causes an increased fructose uptake, an increased formation of sorbitol and glycerol corresponding to the increase in fructose uptake, decreased lactate, and pyruvate output, and an increase in glucose and acetate output (11). Ethanol inhibits the metabolism of glycerol by the liver and leads to an accumulation of alpha-glycerophosphate in the liver (12). Rat liver slices showed the highest formation of glycerol and the highest concentration of alpha-glycerophosphate in media containing fructose and ethanol. D-Glyceraldehyde increased the rate of ethanol oxidation similar to fructose. Gycerol lowered the rate of ethanol oxidation if fructose and ethanol were both present but had no effect on the rate of ethanol oxidation if glucose and ethanol were both present (13). The interaction of fructose and ethanol metabolism might be an example of catalytically coupled reactions. The production of glycerol from D-glyceraldehyde (*reaction 4*) or lactic acid from pyruvic acid (*reaction 5*) could generate NAD+, which could then accelerate the formation of acetaldehyde and its further oxidation to acetic acid with the generation of NADH. The NADH in turn would then accelerate these same reactions. The coupling of glyceraldehyde metabolism with that of ethanol has been proposed as a mechanism for the influence of fructose on ethanol oxidation (14).

It is interesting that D-glyceraldehyde is metabolized by glyceraldehyde-3-phosphate dehydrogenase to form glyceric acid. This reaction is inhibited by Antabuse (tetraethylthiuram disulfide) (15). D-Glyceraldehyde also inhibits rabbit muscle glyceraldehyde-3-phosphate dehydrogenase. This may be the mechanism whereby it inhibits glycolysis (16). It is known that when large amounts of fructose are fed to normal rats a loss in the capacity to utilize glucose occurs and that this is not reversed by insulin

treatment. This effect was demonstrated after feeding fructose for 3 days. The site of impairment was localized to the liver (17). A similar result occurs in the dog fed a high fructose diet (18). This may be due to the lack of induction of glucokinase by fructose (19). How rapidly such an effect can occur has not been studied.

The catalytically coupled reactions relate to the acute utilization of fructose. The long-term feeding of fructose is known to alter hepatic enzyme levels (20, 21) so that the steady state rate of conversion of fructose to lactic acid may be altered considerably.

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